“Is That Muscle Contracture or Are You Just Happy to See Me?”

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Introduction

Tetanus is a relatively uncommon neuromuscular disorder in canines caused by the bacteria *Clostridium tetani*. Because this species of clostridium is an obligate anaerobe, it becomes highly pathogenic in low-oxygen environments due to optimal conditions for sporulation and subsequent neurotoxin release.[1] Unlike other neuromuscular junction diseases such as botulism and myasthenia gravis which result in muscle weakness, canine tetanus infections can lead to spastic paralysis, or rather, sustained muscle contraction without relaxation.[4] In veterinary medicine, tetanus infections typically occur following exposure to the organism by means of a penetrating wound, burn, or surgical contamination.[1] Relative to some large animal species, canines are less susceptible to tetanus and the incidence of infection is much lower. Regardless, the goals of treatment are very similar. Due to the severity and rapidly progressing nature of the disease, any animal suspected of having tetanus must be immediately addressed with aggressive treatment, even in the absence of a definitive diagnosis.

History and Presentation

Grace is an approximately 7-year-old female spayed Labrador Retriever who presented to Mississippi State University College of Veterinary Medicine Emergency Service on 11/17/21 for ataxia, bilateral third eyelid elevation, and a wound on the third digit of her left forelimb. She had a history of a non-weightbearing lameness of 3–4-day duration following a duck hunting trip with her owner the week prior. She was seen by her primary veterinarian on 11/16/21 who suspected a tetanus infection and administered subcutaneous penicillin and oral metronidazole before referring to MSU-CVM for further work-up.

On initial presentation, Grace was bright, alert, and anxious. She weighed 26 kilograms with a body condition score of 6/9. Her vitals were normal with a heart rate of 72 beats per

minute, panting for a respiratory rate, and a rectal temperature of 101.1 degrees Fahrenheit. She had bilateral third eyelid elevation, bilateral scleral injection, as well as moderate contraction of her facial muscles. A wound on the medial surface of the third digit on the left forelimb was present, as well as moderate soft tissue swelling of the affected digit. She appeared mentally appropriate but displayed mild photophobia and tactile hyperesthesia. On cardiothoracic auscultation, no murmurs, wheezes, or arrhythmias were appreciated. Her mucous membranes were pink and moist with a capillary refill time of less than two seconds. She had a mild skin tent and was estimated to be about 5% dehydrated. The remainder of her triage exam was unremarkable.

A baseline CBC and chemistry performed with Grace's primary veterinarian were both within normal limits. A creatinine kinase performed by the emergency service was also normal. Radiographs of her left manus revealed a fracture of the ungual process of the third phalanx with associated soft tissue swelling. A sterile culturette was used to obtain a sample of her wound and was submitted for an aerobic culture and sensitivity + anaerobic culture.

Pathophysiology

Clostridium tetani is a ubiquitous, spore-forming organism that can be found in soil and feces of animals and humans. Clinical signs of tetanus occur on average 5-10 days after inoculation of the organism; however, it has been found that the closer the initial tissue insult is to the central nervous system, the shorter the incubation period and the poorer the prognosis.[5] When these dormant (inactive) spores are introduced to animal tissue, and thus in an anerobic environment, they undergo sporulation and form vegetative (active) endospores. These endospores produce two toxins, tetanolysin and tetanospasmin, but only the latter is responsible for the typical neurologic signs seen with tetanus infection.[1] Tetanospasmin works by entering

inhibitory interneuron cells known as Renshaw cells. Renshaw cells form a synapse with alpha motor neurons, which are lower motor neurons responsible for innervating skeletal muscle and causing contraction. Tetanospasmin disrupts Renshaw cells by cleaving snare proteins, which then prevents the release of glycine and GABA, both inhibitory neurotransmitters. When Renshaw cells fail, the alpha motor neuron continues to fire without any inhibitory control, thus causing continuous muscle rigidity and spasm. This neuronal inhibition blockade is irreversible and requires regeneration of axon terminals to return to function, a process that may take up to three weeks. [1]

Although there are four forms of tetanus described in humans, only two have been reported in animals: localized and generalized. Localized tetanus infections are usually associated with lower toxin burdens and lower mortality rates.[1] Spasm and rigidity are typically observed in a limited area of the body with localized tetanus. The opposite is true of generalized tetanus infections, which are characterized by extreme and diffuse muscle rigidity and early cranial nerve involvement.[3] Autonomic dysfunction may also occur but is infrequently described in animals.

Diagnostic Approach

Diagnosis of canine tetanus is predominantly based on history and clinical signs. Specifically, a recent history of a penetrative injury, burn, or surgical procedure coupled with appropriate clinical signs would be adequate to institute treatment for tetanus. Classic clinical signs of canine tetanus include protrusion of the third eyelid, trismus (lockjaw), risus sardonicus (sardonic grin), hyperesthesia, hypersensitivity to auditory stimuli, dysphagia, ptyalism, altered facial expression, and generalized muscle rigidity with spastic tetraplegia.[1] On physical examination, there may be an obvious increase in muscle tone with episodic muscle spasms.

While it would not be wrong to perform ancillary diagnostics on a dog suspected of having tetanus, affected animals often have no changes in blood work values.[1] A complete blood count may reveal a neutrophilic leukocytosis while a chemistry panel may reveal elevated creatinine kinase (CK) and aspartate aminotransferase (AST) levels. Additionally, a bacterial culture of the wound may be performed; however, isolation of *Clostridium tetani* has been reported to be successful only 30% of the time in humans.[5]

Because tetanus is a clinical syndrome that is often not accompanied by laboratory abnormalities, it is imperative to rule out other possible causes. As with any patient exhibiting neurologic signs, rabies should always be included in list of differentials. Other important rule outs include neurologic toxicities (organophosphates, strychnine, metaldehyde), hypocalcemia, meningoencephalitis, immune-mediated polymyositis, cerebellar disease, spinal trauma, and drug reactions.[2]

Treatment and Management

Goals of therapy for the canine tetanus patient include neutralizing circulating toxins, inhibiting further growth of *C. tetani* by the administration of appropriate antimicrobials, reducing muscle spasms with sedatives, debriding the wound (if applicable), and providing supportive care until the effects of the toxin have diminished.[1,2]

While tetanus antitoxin is regarded as a critical component for the treatment of canine tetanus infections, there have been few studies demonstrating the difference of survival for animals treated with and without immunoglobulin therapy. There are currently two types of tetanus antitoxins available for the treatment of tetanus in animals: human tetanus immunoglobulin (TIG) and equine anti-tetanus serum (ATS).[1] Tetanus immunoglobulin therapy is implemented for the purpose of neutralizing circulating toxins in the blood of an animal;

however, it quickly become ineffective once the toxin infiltrates the central nervous system as neither TIG nor ATS can cross the blood-brain barrier. Appropriately dosing antitoxin in animals with tetanus may be difficult because effective doses depend on the amount of toxin needing to be neutralized (as opposed to dosing based off the size of the patient). For this reason, a wide dosing range of 100-1,000U/kg with a maximum dosage of 20,000 has been established for animals.[1] Because TIG and ATS are both foreign biologics to the canine, adverse effects have been documented with tetanus antitoxin administration including anaphylaxis, anaphylactoid reactions, and serum sickness. Due to the limitations and possible adverse effects associated with its usage, administration of tetanus antitoxin should be considered on a case-by-case basis.

Antimicrobials are the mainstay of canine tetanus therapy. While appropriate antimicrobials have no effect on circulating toxins, they may prevent further toxin formation by eliminating clostridial spores.[1] Although various antimicrobials have been shown to be effective against *Clostridium tetani*, several studies have demonstrated metronidazole to be the drug of choice.[2,8] In a study conducted by Ahmadsyah et al, metronidazole was shown to be superior to procaine penicillin in human patients due to greater anaerobic tissue penetration, mortality reduction, and reduced hospital stay duration.[8] A loading dose of 15mg/kg followed by a maintenance dose of 20-30mg/kg IV (or PO in mild cases) for 7-14 days is the recommended protocol for metronidazole in canine tetanus patients. If metronidazole is unavailable, penicillin 20-100,000 iu/kg BID, amoxicillin-clavulanate 12mg/kg BID, clindamycin 3-10mg/kg BID, or tetracycline 22mg/kg TID may be instituted as alternative antimicrobial therapy.[4]

Managing spastic paralysis, without interfering with voluntary motor function, is a critical component of canine tetanus therapy. Benzodiazepines such as diazepam have been shown to be advantageous over similar drugs (such as methocarbamol and acepromazine) due to

its combined muscle-relaxant, anticonvulsant, and anxiolytic properties.[2] Additionally, human studies have demonstrated that diazepam administration was associated with a milder clinical course of the disease, shorter hospitalization time, and better chance of survival.[6] In more recent literature (both human and veterinary), magnesium sulfate has been used as an adjunct therapy in managing muscle spasms associated with generalized tetanus.[9] While the absolute efficacy of magnesium therapy has yet to be established, supraphysiologic levels of magnesium have been shown to aid with muscle relaxation in tetanus patients. The benefits of muscle relaxation by means of magnesium supplementation are that the effects are more manageable, there is little concern for respiratory depression, and it allows for a dose reduction for other drugs (such as diazepam).[7,9]

Additional supportive measures such as wound care, environmental control, and nutritional and respiratory support must be considered for canine tetanus patients. If applicable, wound debridement is recommended to remove non-viable tissue, eliminate surface bacteria, and encourage wound healing.[2] While in hospital, it is also advised to bandage the wound as to prevent secondary infections. As some patients will exhibit hypersensitivity to auditory, visual, and tactile stimuli, it is imperative that these patients be kept in a dark, quiet area with as minimal handling as possible. This control measure is to reduce the incidence of muscle spasms, as any stimulus may be a trigger.[1] In mild or early cases of canine tetanus, such as Grace's, nutritional and respiratory support may not be necessary. However, for an animal with advanced clinical signs such as trismus and dysphagia, assisted feeding by means of a nasogastric/nasoesophageal tube or esophagostomy tube may be necessary to ensure the patient is receiving adequate nutrition. Similarly, for patients with advanced clinical signs and subsequent respiratory compromise, mechanical ventilation may be indicated. Human studies

have demonstrated reduced mortality with early intervention ventilatory support. Unfortunately, mechanical ventilation is often limited by economic restraints in veterinary medicine.[1]

Prognosis for canine tetanus infections is largely determined by the severity of clinical signs at the time of presentation and the distribution of the disease (localized versus generalized).[1] Human studies have identified additional prognostic factors such as delay in treatment, nosocomial infections or concurrent disease, and history of immunization (unavailable for canine patients) .[10] Additionally, localized tetanus infections have been shown to have lower mortality rates relative to generalized tetanus infections due to a lower toxin burden.[1] With all factors considered, a dog diagnosed with tetanus early in the disease process that is promptly provided with appropriate treatment has a good prognosis for survival.

Case Outcome

Following presentation and initial work-up, Grace was started on intravenous fluids at a maintenance rate of 65ml/hr and Unasyn 30mg/kg IV TID. She was transferred to the internal medicine service the next day and the following medications were added to her treatment regimen: metronidazole 10mg/kg IV BID, clindamycin 23mg/kg PO BID, gabapentin 12mg/kg PO TID, Trazodone 4mg/kg PO TID, and 1 capsule of Proviable PO SID. Because her inciting injury was greater than 10 days old, she was not a candidate for antitoxin therapy.[4]

Grace was kept in a dark and quiet corner of ICU to limit stimuli. Per the recommendation of MSU-CVM's surgery service, her injured paw was soaked in a chlorhexidine solution once daily and then re-bandaged with a Robert Jones bandage as to keep the wound clean and avoid secondary infection. After five days in hospital, she was eating and drinking well enough to transition to all oral medications and discontinue intravenous fluids. The culture of her wound isolated three different bacterial species: *Bacillus cereus, Enterococcus faecium,* and

Clostridium sordelli. Despite these results, Grace continued to be treated for tetanus given the documented poor success at identifying *Clostridium tetani* in surface wounds.

Due to the lack of disease progression observed in hospital, Grace was discharged to her owner for continued supportive care. She was sent home with a 30-day course of Clavamox, clindamycin, metronidazole, gabapentin, trazodone, and Proviable. Two months after discharge, Grace's owner reports that she is doing well and is living her best life as a duck dog.

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